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Catalytic Asymmetric Epoxidation of Electron-Deficient Enynes Promoted by Chiral *N,N'*-Dioxide-Scandium(III) Complex

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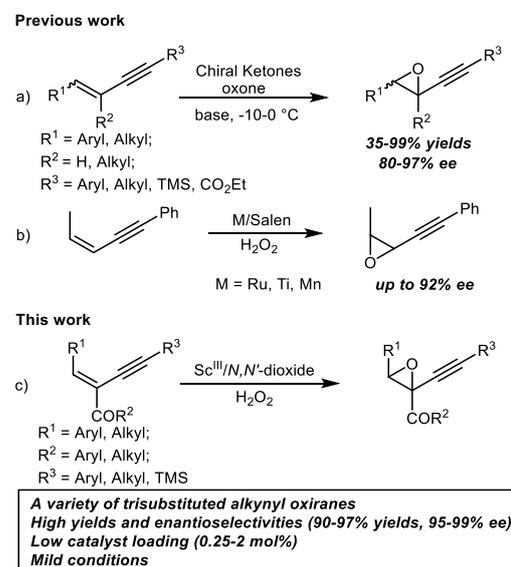
Abstract. An asymmetric epoxidation of electron-deficient enynes with environmentally benign aqueous hydrogen peroxide as oxidant has been accomplished by developing a chiral *N,N'*-dioxide-Scandium(III) complex catalytic system. In the presence of 0.5-2 mol% catalyst, a variety of trisubstituted alkynyl oxiranes were obtained in high yields (up to 97%) with excellent *ee* values (up to 99%). Furthermore, control experiments provide a fundamental insight into the reaction mechanism.

Keywords: asymmetric catalysis; epoxidation; electron-deficient enynes; *N,N'*-dioxide; Scandium(III)

Chiral epoxide compounds are versatile intermediates and building blocks in organic synthesis. Since a milestone achievement was obtained by Sharpless for the asymmetric epoxidation of allylic alcohols in the early 1980s,^[1] much progress has been made towards these optically pure compounds.^[2, 3, 4, 5] Chiral alkynyl oxiranes, one type of them, are useful motifs in numerous biologically active natural and unnatural compounds.^[6] They are also important synthetic intermediates for a wide range of derivatives.^[7] Over the past few years, many strategies have been devoted to their synthesis.^[8] Among them, enantioselective epoxidation of enynes provides a direct approach to chiral alkynyl oxiranes. Shi applied their fructose-derived ketones as catalysts to efficiently promote the epoxidation of enynes with oxone as oxidant and give the products in good yields and *ee* values (Scheme 1a).^[9] On the other hand, aqueous hydrogen peroxide is probably the most competitive oxidant for its advantage of cheapness, high atom efficiency and generating water as the sole by-product. The epoxidation of unfunctionalized enynes using H₂O₂ as oxidant catalyzed by chiral salen-metal catalysts were efficient (Scheme 1b).^[10] However, there was still no report on the highly enantioselective epoxidation of trisubstituted enynes with electron-deficient groups. In this regard, a suitable oxidant and catalyst should

be established to furnish a highly chemoselective epoxidation of the functionalized enynes.^[11]

Chiral *N,N'*-dioxides developed by our group, can coordinate with various metal salts to form the complexes, which have been proved to be efficient in a number of asymmetric transformations.^[12] As an ongoing work in the epoxidation reaction,^[13] here we developed a highly efficient asymmetric epoxidation of electron-deficient enynes with a low catalyst loading to 0.5 mol%, giving a variety of trisubstituted alkynyl oxiranes in high yields (90-97%) and excellent enantioselectivities (95-99% *ee*) (Scheme 1c).



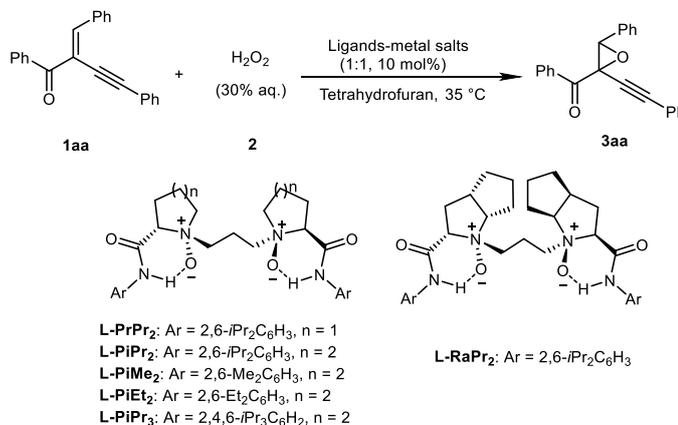
Scheme 1. Direct asymmetric epoxidation of conjugated enynes.

In the beginning, the enyne **1aa** was chosen as the model substrate and aqueous hydrogen peroxide as the oxidant to optimize the reaction conditions. Initially, a series of metal salts complexing with chiral *N,N'*-dioxide **L-PrPr₂** was explored. Many

metal complexes, such as the $\text{Zn}(\text{OTf})_2$ or $\text{Mg}(\text{OTf})_2$ complex, could not promote the reaction (Table 1, entries 1 and 2). Fortunately, lanthanide metals,

$\text{Tb}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$ could give high enantioselectivity though the yield was low. Since

Table 1. Optimization of the reaction conditions.^[a]



Entry	Metal salts	Ligand	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	$\text{Zn}(\text{OTf})_2$	L-PrPr₂	n.r. ^[d]	-
2	$\text{Mg}(\text{OTf})_2$	L-PrPr₂	n.r.	-
3	$\text{Tb}(\text{OTf})_3$	L-PrPr₂	35	92
4	$\text{Sc}(\text{OTf})_3$	L-PrPr₂	36	94
5	$\text{Sc}(\text{OTf})_3$	L-PiPr₂	95	99
6	$\text{Sc}(\text{OTf})_3$	L-RaPr₂	61	98
7	$\text{Sc}(\text{OTf})_3$	L-PiMe₂	88	97
8	$\text{Sc}(\text{OTf})_3$	L-PiEt₂	93	98
9	$\text{Sc}(\text{OTf})_3$	L-PiPr₃	90	99
10 ^[e]	$\text{Sc}(\text{OTf})_3$	L-PiPr₂	95	99
11 ^[f]	$\text{Sc}(\text{OTf})_3$	L-PiPr₂	88	99

[a] Unless otherwise noted, all the reactions were carried out with ligand/metal salts (1:1, 10 mol%), **1aa** (0.1 mmol), **2** (0.3 mmol) in THF (Tetrahydrofuran, 0.5 mL) at 35 °C for 16 h.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.

[d] No reaction.

[e] The reactions were carried out with **L-PiPr₂**/metal salts (1:1, 0.5 mol%), **1aa** (0.6 mmol), **2** (1.8 mmol) in THF (1.0 mL) at 35 °C for 48 h.

[f] 0.25 mol% catalyst was used and the concentration of **1aa** was 0.8 M.

$\text{Sc}(\text{OTf})_3$ gave a little higher yield and *ee*, we next chose $\text{Sc}(\text{OTf})_3$ to explore chiral *N,N'*-dioxide ligands. It was found that the bulky amide subunits of the ligands have a great influence on the reactivity and enantioselectivity of the reaction. Both (*S*)-pipercolic acid derived **L-PiPr₂** and (*L*)-ramipril derived **L-RaPr₂** could give the better results. Especially, (*S*)-pipercolic acid derived **L-PiPr₂** improved the activity sharply, offering the product in 95% yield after 16 h. Meanwhile, the enantioselectivity was also increased to 99% *ee* (Table 1, entries 4-6). The substituent at the amide moiety of the ligands was also investigated showing that the yield would decrease gradually as the steric hindrance was reduced (Table 1, entries 7-9). To our delight, the catalyst loading could be reduced to 0.5 mol%, and the same yield and *ee* value were maintained when the concentration of **1aa** was

increased to 0.6 M and prolonging the reaction time to 48 h (Table 1, entry 10). When the catalyst loading was further decreased to 0.25 mol%, the optical active product could be still obtained albeit in a little lower yield by increasing the concentration of substrate to 0.8 M (Table 1, entry 11).

With the optimal conditions established (Table 1, entry 10), the substrate scope was investigated. As shown in Table 2, a variety of electron-deficient enynes were tolerated. The reactivities and enantioselectivities were influenced little by different substituents at the aromatic ring (Table 2, entries 1-4). When the substituent at aromatic ring R^2 was varied, the electronic and steric effect have no significant effect (Table 2 entries 5-12). When R^2 was trimethylsilyl group, the high yield and *ee* value were obtained (Table 2 entry 13). If it was replaced by the

cyclopropyl or propyl groups, lower yields could be overcome by increasing the catalyst loading to 2 mol% (90% yields, 99% *ee*; Table 2, entries 14 and 15). Besides, whether R¹, R³ were alkyl or phenyl

Table 2. Substrate scope of electron-deficient enynes of the asymmetric epoxidation.^[a]

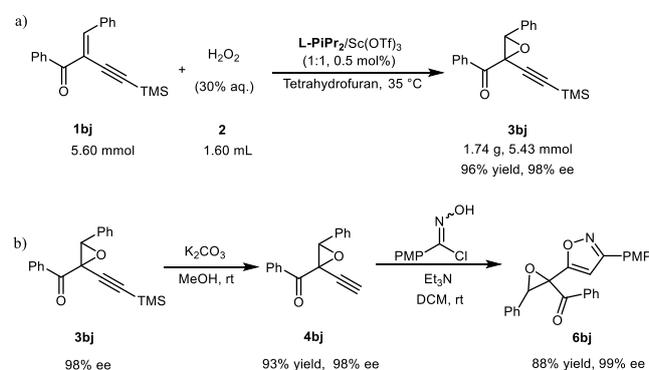
Entry	R ¹	R ²	R ³	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	Ph	Ph	Ph	95 (3aa)	99
2	4-ClC ₆ H ₄	Ph	Ph	96 (3ab)	98
3	4-BrC ₆ H ₄	Ph	Ph	93 (3ac)	99
4	4-MeC ₆ H ₄	Ph	Ph	96 (3ad)	99
5	Ph	2-FC ₆ H ₄	Ph	97 (3ba)	99
6	Ph	3-FC ₆ H ₄	Ph	93 (3bb)	99
7	Ph	4-FC ₆ H ₄	Ph	93 (3bc)	99
8	Ph	4-ClC ₆ H ₄	Ph	95 (3bd)	99
9	Ph	4-BrC ₆ H ₄	Ph	96 (3be)	99
10	Ph	4-MeC ₆ H ₄	Ph	97 (3bf)	98
11	Ph	3-MeC ₆ H ₄	Ph	94 (3bg)	99
12	Ph	4- ^t BuC ₆ H ₄	Ph	97 (3bh)	99
13	Ph	TMS	Ph	96 (3bi)	98
14 ^[d]	Ph	Cyclopropyl	Ph	90 (3bj)	98
15 ^[d]	Ph	Propyl	Ph	90 (3bk)	99
16 ^[d]	Ph	Ph	Me	93 (3ca)	97
17 ^[d]	Ph	Ph	ⁿ Bu	95 (3cb)	96
18 ^[d]	Ph	TMS	Me	94 (3cc)	99
19 ^[d]	Ph	TMS	ⁿ Bu	95 (3cc)	99
20	Ph	Ph	4- ^t BuC ₆ H ₄	93 (3da)	99
21	Ph	Ph	3-ClC ₆ H ₄	97 (3db)	99
22 ^[d]	Propyl	Ph	Me	96 (4aa)	95

[a] Unless otherwise noted, all the reactions were carried out with **L-PiPr₂/Sc(OTf)₃** (1:1, 0.5 mol%), **1** (0.6 mmol), **2** (1.8 mmol) in THF (Tetrahydrofuran, 1.0 mL) at 35 °C for 48 h.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.

[d] The reactions were carried out with **L-PiPr₂/Sc(OTf)₃** (1:1, 2 mol%), **1** (0.3 mmol), **2** (0.9 mmol) in THF (0.5 mL) at 35 °C for 48 h.



Scheme 2. Gram-scale version and the derivatives.

groups, all the reactions could give the products in high yields (90-97%) with excellent

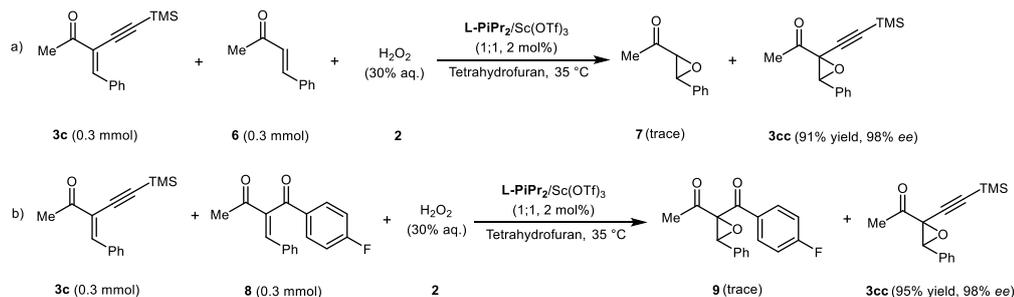
enantioselectivities (Table 2, entries 16-22). Finally, The absolute configuration of the 4-bromo-substituted product **3ac** was determined to be (2*S*, 3*R*) by X-ray crystallographic analysis.^[14]

To show the synthetic utility of the method, a gram-scale synthesis of **3bj** was performed. As shown in Scheme 2a, in the presence of 0.5 mol% catalyst, 5.60 mmol of the enyne substrate **1bj** transformed to the corresponding product **3bj** in 96% yield (1.74 g) with 98% *ee*. Meanwhile, the trimethylsilyl group of the product **3bj** could be easily deprotected to transform into **4bj** in 93% yield with 98% *ee* (Scheme 2b) Moreover, **4bj** could readily undergo a cycloaddition with *N*-hydroxyl benzimidoyl chloride to give the product isoxazolidine **6bj** (88% yield, 99% *ee*, Scheme 2b).

In order to gain an insight into the roles of alkynyl group in the reaction, control experiments were performed (Scheme 3). Firstly, the competition

reaction of benzylideneacetone **6** and enyne substrate **3c** was conducted under standard conditions. The optical active alkynyl oxirane product **3cc** was obtained in excellent yield and *ee* value, and trace amount of the epoxidation product **7** was detected (Scheme 3a). Subsequently, another competition experiment between enyne **3c** and 1,3-dione substrate **8** was performed. Still, only the epoxidation product of enyne **3c** was obtained (Scheme 3b). It indicated that alkynyl groups might make the substrates more reactive, not only featuring an electron-withdrawing moiety.^[15, 16] On the basis of the control experiments,

the X-ray structure of the product **3ac** and the previous work,^[16] a possible catalytic model was proposed to elucidate the origin of the stereoselectivity. As outlined in Figure 2, the enyne substrate coordinated to the scandium complex in a bidentate fashion. The *Si* face of the enyne **1ac** was shielded by the nearby isopropylphenyl group of the *N,N'*-dioxide. So the peroxide attacked the β -carbon atom of the Michael acceptor enyne **1ac** preferably from the *Re* face, and the product alkynyl oxirane formed.



Scheme 3. The control experiments.

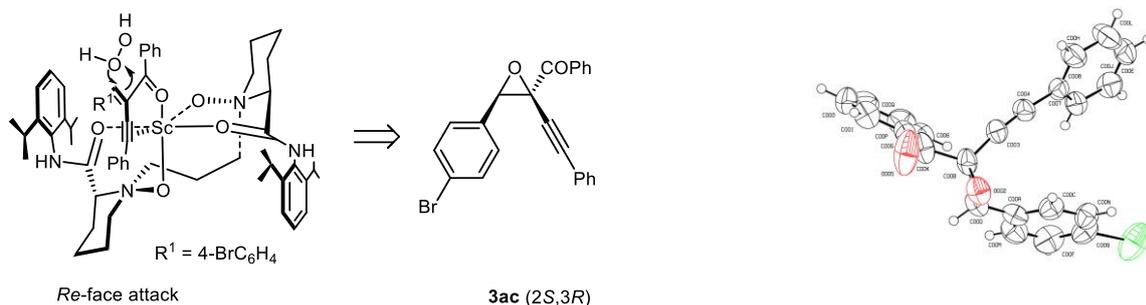


Figure 1. Possible catalytic model and X-ray structure of the product **3ac**.

In summary, the asymmetric epoxidation of electron-deficient enynes was accomplished with aqueous hydrogen peroxide as oxidant by using a low catalyst loading of an effective chiral *N,N'*-dioxide-scandium(III) complex catalyst. A variety of trisubstituted alkynyl oxiranes were obtained in excellent yields (90-97%) and *ee* values (95-99%). Over the control experiments, the alkynyl groups might make the substrates more reactive through coordinating to the scandium complex, not only featuring an electro-withdrawing moiety.

Experimental Section

In an oven-dried reaction tube with a magnetic stirring bar, $\text{Sc}(\text{OTf})_3$ (0.5 mol%), **L-PiPr**₂ (0.5 mol%), electron-deficient enyne **1aa** (0.6 mmol) in THF (Tetrahydrofuran, 1.0 mL) were stirred at 35 °C for 0.5 h at N_2 atmosphere. Then hydrogen peroxide (170 μL , 1.8 mmol, 30% w/w in H_2O) was added, and the reaction mixture was stirred at 35

°C for 48 h. The reaction mixture was directly purified by flash column chromatography (ethyl acetate/petroleum ether = 1/30) to afford the desired product. The enantiomeric excess was determined by chiral HPLC and the product propargyl oxirane was determined by NMR analysis.

Acknowledgements

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